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Research Article

Elucidating fungicide complex formation mechanisms with *Phytophthora infestans* target proteins: In silico insights

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Abstract

The development of new pesticides as well as new approaches in their application are important challenges for food security. Currently, bioinformatics methods are useful for searching and designing models of molecular target structures, including antiviral, fungicidal, bactericidal, insecticidal, herbicidal drugs and plant growth regulators, which have been recently used in agrochemical research. In this article, we present the findings of a study investigating the molecular mechanisms underlying the binding of fungicides (fluopicolide, propamocarb) to target proteins (cytochrome P450, glutathione-S-transferases) of *Phytophthora infestans*. Virtual three-dimensional complexes of pesticides and their targets have been created using bioinformatics methods. A new approach for identifying the cavity parameters of binding sites using machine learning technology has been proposed. Rigid docking of pesticides with targets has been carried out and the binding energy calculation showed a high degree of stability of ligand-protein complexes. Our proposed *in silico* approach may be useful for studying the molecular mechanisms of fungicides action on *Phytophthora* proteins.

Key words: Bioinformatics, fluopicolide, fungicides, ligand, pesticides, propamocarb, target, target enzyme

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Introduction

The development of new pesticides as well as new approaches in their application are important challenges for food security. From the economic point of view, the development of new pesticides is not a cheap process, as it requires a lot of money and time to conduct laboratory and field research and testing of the efficacy and safety of the preparations. It is estimated that it

takes up to 250–280 million USD and about 10 years to develop a single synthetic pesticide and bring its synthesis to production scale (Marrone 2014; McDougall 2016).

One of the approaches to reduce time, money and other costs is the use of computational biology methods. For example, bioinformatics methods are useful for searching and designing models of molecular target structures, including antiviral, fungicidal, bactericidal, insecticidal, herbicidal drugs and plant growth regulators, which are currently used in agrochemical research (Li et al. 2020). Structure-based molecular design and optimization methods are being developed and also applied to find new fungicides. For example, novel inhibitors of the mitogen-activated protein kinase FgGpmk1, which plays a vital role in the development and virulence of *Fusarium graminearum*, the causative agent of Fusarium head blight, were discovered using *in silico* methods (Fu et al. 2021).

Species of *Phytophthora* are among the major pathogens in the agricultural industry today. The genus has about 200 species and is probably the most economically important in the field of plant pathology (Brasier et al. 2022). Various fungicides (protective, translaminar, curative, systemic, antisporulants) are used against *Phytophthora*, but *Phytophthora* populations are able to develop resistance to these agents (Ivanov et al. 2021). This forces us to search for the development of new fungicides or modernization of the existing ones.

The target organism for this study was selected as a typical pathogen of *Phytophthora infestans*. No information on target proteins of the fungicides under study and specific target proteins of *P. infestans* could be found in the scientific literature. At the same time, it is known that cytochrome P450 enzymes (heme-containing monooxygenases; hereinafter CYP450) play a crucial role in the biology and ecology of fungi (Park et al. 2008). In particular, proteins of the CYP450 system of *Phytophthora capsica* are involved in the system of development of resistance to fungicides (Dai et al. 2022). Glutathione-S-transferase (hereafter GST) proteins in *P. infestans* may be involved in fungicide resistance and are actively expressed during infection of potato plants (Bryant et al. 2006). Therefore, we selected CYP450 and GST proteins of *P. infestans* as the targets.

Fluopicolide and propamocarb have been chosen to study the molecular features of interaction of fungicides with proteins of the target organism. These are typical fungicides against Phytophthora that are used in experimental field farms. Fluopicolide is a synthetic fungicide of the benzamide group, and is characterized by its ability to delocalize spectrin-like proteins. Propamocarb is a synthetic carbamide fungicide with the function of inhibiting lipid synthesis. Both pesticides have been developed to control oomycetes including Phytophthora, some *Pythium* species, root rot on various crops (grapes, hop, potatoes, various vegetables and others).

At the same time, there are few works in the academic environment to study the properties of propamocarb on various model objects. For example, one study investigated the ability of propamocarb to form stable bonds with human estrogens in complex with agonists/antagonists to study toxic effects (Celik et al. 2008). Recent work from 2021 used in silico methods to evaluate the ability of propamocarb to bind to toxins of the oomycete *Pythium splendens*, to deactivate them (Reghu 2021). We did not find any information on the study of fluopicolide using the methods of modeling intermolecular interaction.

In the above studies, the target proteins CYP450 and GST in *P. infestans* were not considered as a model object. This makes it possible to apply a new approach of using molecular docking on direct targets of the *Phytophthora* pathogen.

Here we present the results of our investigation of fungicides using advanced *in silico* methods. Specifically, we used molecular docking techniques to study the interaction of propamocarb and fluopicolide with CYP450 and GST target proteins. Our study aimed at illuminating the molecular mechanisms underlying the interactions between these fungicides and their respective target proteins. Using computational modeling, we aimed at gaining valuable information on the potential binding affinity and structural aspects of these interactions, which may be important for understanding the efficacy and action of these fungicides against plant pathogens.

Material and methods

In silico methods for screening

Structural and functional data of fungicides were extracted from the Pesticide Target Interaction Database (Gong et al. 2013) and Pesticide Properties DataBase (Lewis et al. 2016). Three-dimensional structure data for fluopicolide and propamocarb ligands were imported from the Pubchem database.

Information on the structural-functional design of proteins was taken from the UniProtKB database (https://www.uniprot.org/). Polypeptide structures of CYP450 and GST in pdb format (protein data bank) were searched in the database. Proteins maximally annotated in terms of transmembrane domains and binding sites were selected for docking. In the UniprotKB database at the moment of access (30.12.2023), 101 forms of CYP450 (selected protein ID: A0A833SPT7) and 29 forms (not including separate annotated C- and N-terminal sites) of glutathione S transferase (selected ID: D0NL97) of *P. infestans* were represented.

In silico methods for docking

The search for molecular cavities and coordinates of their centers, as well as modeling of molecular interaction, was performed using the approach we developed. The approach combines the prediction of binding cavities by the P2Rank algorithm (PrankWeb) and validation of these results by BLAST-alignment of reference proteins with annotated homologous structures, which allows us to optimize calculations and increase the accuracy of prediction results.

Typically, approaches developed for predicting molecular cavities are based on various score metrics, existing physicochemical algorithms, or the use of neural networks. Such solutions allow for the rapid identification of geometric figures representing molecular cavities in which the ligand may be located. Initially, the molecular docking method was developed specifically to search for such cavities, but over time, with the growth of technology, this method began to perform the role of refining the topology of the ligand in an already found cavity, as well as identifying key amino acid residues involved in binding.

Such an algorithm has proven itself well when working with proteins that have a high level of annotation, whose three-dimensional structures were obtained experimentally. However, when working with proteins obtained by the homology method or using neural networks such as AlphaFold and its modifications, we are faced with an extensive pool of biomolecules with a low level of evidence and difficulties in localizing molecular cavities. The cross-validation approach used in our study allows us to smooth out this imprecision by superimposing key amino acid residues found in more annotated homologues onto our target targets. In this way, we can superimpose them onto the predicted cavities. This solution allows us to select the most suitable results, after which the molecular docking method can be used to refine the ligand position.

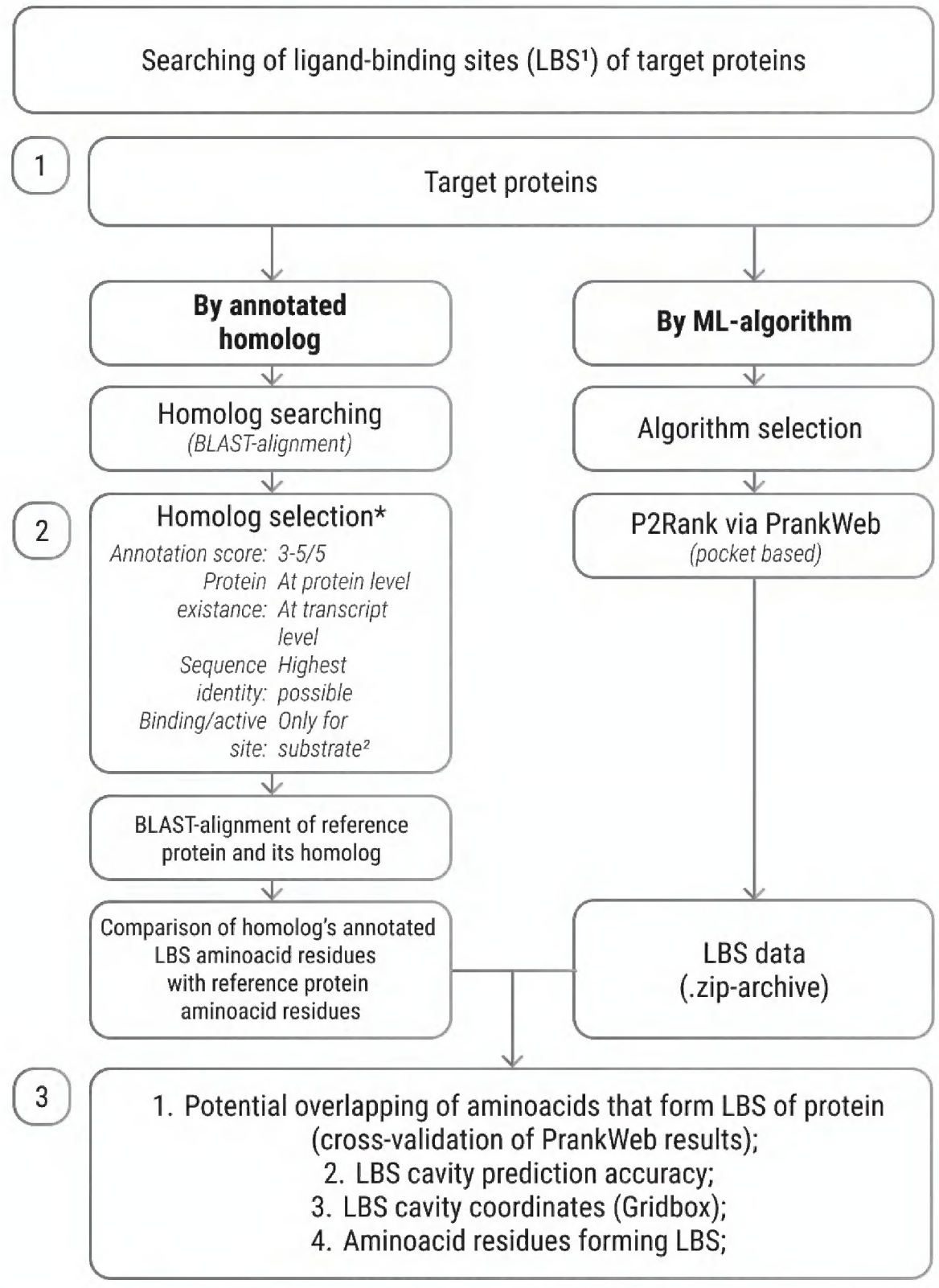
The method of annotated homologs (indicated on the left in the scheme of Fig. 1) is based on the selection of a more annotated homologous structure using BLAST alignment to the amino acid sequence of proteins (performed on the UniProtKB resource). First, a global alignment was performed to find a pool of homologous structures, and then proteins were selected from the pool according to several criteria: annotation score within 3–5/5; protein existence should be confirmed at the proteome/transcriptome level; sequence identity is the highest among the proposed ones (if other criteria are satisfied); substrate binding sites are present (ionic and co-factor ligand-binding sites (LBS) were not considered). In some cases, homologs satisfying the above parameters could not be found, so the criteria were adjusted according to the available structures.

The next step was local alignment and comparison of amino acids annotated as LBS in homologs and reference structures. In case annotated protein homologs were not available, we used only ML-algorithm data (machine learning), since the use of a random homolog produces uninformative results when aligned to the primary structure.

The ML algorithm method for finding the LBS of a protein is based on the PrankWeb web server (Jendele et al. 2019). This service was chosen based on several criteria: highly informative prediction result, and open access to the resource, user-friendly interface. In addition, the authors of the server point out that the cavity-based LBS search model performs more efficiently (yields more correctly identified sites when compared to experimentally identified sites), compared to similar services, and also minimizes the prediction of random ligand-binding amino acid residues. The essence of ML-algorithm application is to load the structure of reference protein in pdb-format and specify the desired chain. The output result was an archive with files describing both numerical and graphical prediction data. Among the obtained data, the following parameters were selected: prediction rank (the highest was selected); prediction probability/accuracy (the highest was selected); coordinates of the center of the molecular cavity (Gridbox); amino acids forming this molecular cavity.

The use of two different methods for determining LBS within a common methodology is based on their complementary nature. Amino acid residues of the binding site determined by the homology method can be located within the cavity predicted by the ML algorithm, which, in turn, serves as an additional specification of the location of the LBS.

Based on the results of the LBS search, the coordinates of the molecular cavity of the potential binding site (Gridbox) for subsequent docking were calculated.



* – due to the lack of homologs corresponding to criteria of their selection represented here, they were altered individually
1 – ligand-binding site;
2 – ion-binding and co-factor-binding sites were not taken into account (except individual cases)

Figure 1. General scheme of the algorithm for searching ligand-binding sites of target proteins.

Since in this study it was impossible to predict which amino acid residues of the target protein the ligand should bind to, the method of rigid intermolecular blind docking was chosen for modeling the chemical interaction and checking the affinity of potential ligands to the selected targets. For its implementation we used special standalone programs AutoDock and MGLtools (Morris et al. 2009). MGLtools (version 1.5.6) is a graphical interface that facilitates work with AutoDock (version 4.2).

The first step was to load the target protein into the MGLtools working field, then remove residual water and add a proton to amino acid residues at potential ligand binding sites. In the second step, the ligand was added and a grid (Gridbox) was applied to indicate the docking region. After specifying the grid coordinates, the grid overlay process was started – in autogrid. The result of overlaying is information about the structure of the target protein with indication of the docking region. Since the interaction of fungicides with proteins is

not only electrostatic in nature, and their sizes do not significantly exceed those of classical low molecular weight ligands, Gridboxes in the form of cubes with 40 × 40 × 40Å faces were set up. The third step is to perform the docking itself. To do this, the target and ligand were specified, then the number of docking attempts in the specified region was set (5 attempts for each region). After docking, a dlg-format file with detailed information about the formed complexes (coordinates of the complex location, binding energy, atomic standard deviation, etc.) is created.

Molecular interactions of target proteins with fungicides were modeled using AutoDock automated molecular interaction software (version 4.2). A standard 50-repetition protocol was used for molecular interaction modeling. Subsequently, the results of successful interactions were analyzed. Subsequently, data on ligand conformations were exported to Discovery Studio to obtain 2D and 3D images of ligand-receptor complexes.

All resulting complexes were constructed using PyMol visualization software version 2.5.4 (Schrödinger and DeLano 2020) and afterwards imported and visualized into 2D and 3D images using Discovery Studio Visualizer (version v21.1.0.20298) (BIOVIA 2020).

Results and discussion

Identification of ligand-binding sites (LBS)

During the determination of LBS using the Prank2web service, the coordinates of the sites' cavity center were obtained (Table 1).

The probability value of predicting ligand-binding cavities in the case of the first rank of cavities in terms of percentages was about 29% for GST and 98% for CYP450 (Fig. 2).

The low prediction probability for GST is not related to the quality of folding, as for both proteins it is shown at a predominantly high-quality level (Fig. 3). Thus, very high accuracy of the tertiary structure of GST is noted mainly for alpha-helixes of transmembrane sites (Fig. 3), high accuracy is shown mainly for beta-stacking, and small chain regions with low accuracy are also present. CYP450 also shows a high quality pdb structure with AlphaFold prediction accuracy, where the pLDDT (predicted local distance difference test) index is 80 or more. High stacking quality is characterized for alpha and beta sites, approximately in a 50/50 ratio, with low stacking quality noted for the rest, but a minor portion of the polypeptide chain. The large variation between the accuracy of prediction of molecular cavities in the presented proteins can be explained by the low level of annotation of the tertiary structure of the GST protein.

Conservativity of the polypeptide chains of CYP450 and Phytophthora GST is also not the reason for the low prediction probability for GST. An example

Table 1. Results of determination of the ligand-binding sites of target proteins.

Reference protein, ID UniProtKB	Coordinates of the ligand-binding site cavity center (Gridbox)		
	x_cent	y_cent	z_cent
Cytochrome P450 ID: A0A833SPT7	6.263	0.745	-0.390
Glutathione S transferase ID: D0NL97	-9.820	8.555	1.262

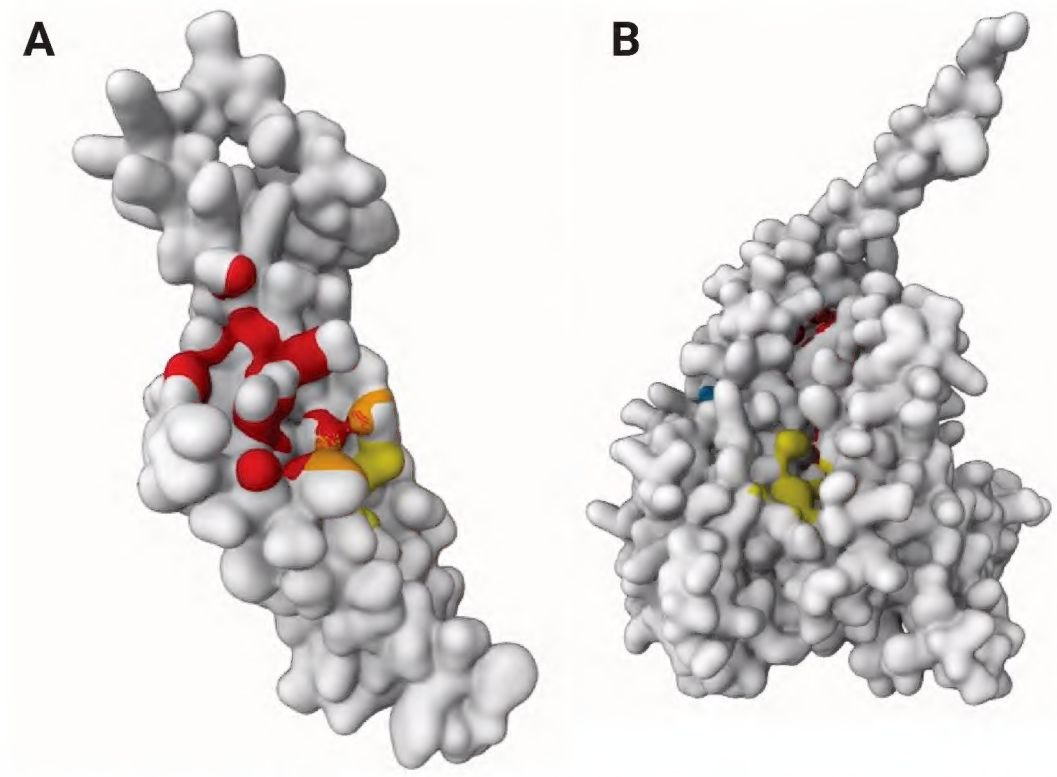


Figure 2. The result of predicting the location of molecular cavities of GST and CYP450 enzymes **A** GST **B** CYP450. The enzymes are depicted as structures with a single molecular surface in gray. Red, yellow, orange, and blue colors mark the regions of polypeptide chains involved in the formation of possible molecular cavities.

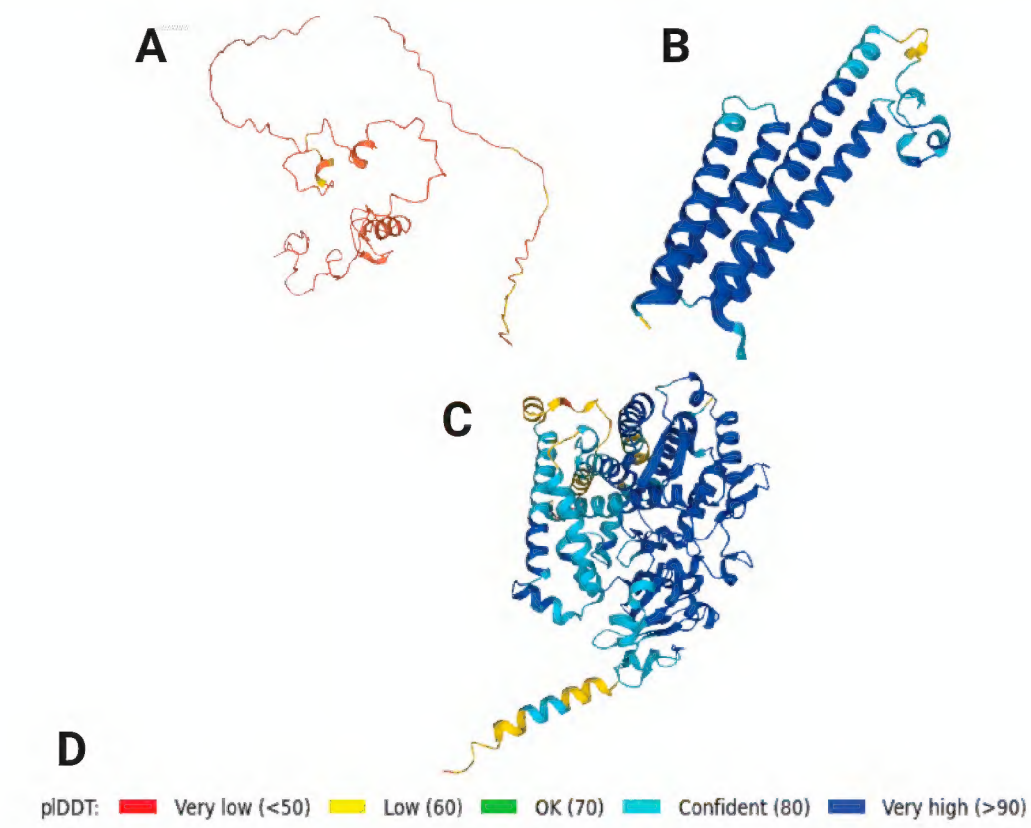


Figure 3. Prediction accuracies of 3D structures using AlphaFold software for **A** metallothionein (given for an example of poor tertiary structure stacking quality) **B** GST **C** CYP450 **D** prediction accuracy expressed by the pLDDT (predicted local distance difference test) index.

of high homology at the 91–97% level of polypeptide sequences of these Phytophthora proteins is shown in Fig. 4.

It is worth noting that we obtained high prediction accuracy for CYP450 protein earlier in the study of interaction between herbicides and weed target proteins (Pamirsky et al. 2023). We also attribute this to the high conservativity of the tertiary structure of the entire cytochrome family, which made it easier for the algorithm to solve the classification task.

Based on the predicted molecular cavities, intermolecular interactions were modeled (Table 2), resulting in the generation of ligand-receptor complexes (Fig. 5).

A total of 21 protein-fungicide complexes (11 for fluopicolide and 10 for propamocarb) with conformation ranks from 1 to 6 were modeled. The maximum

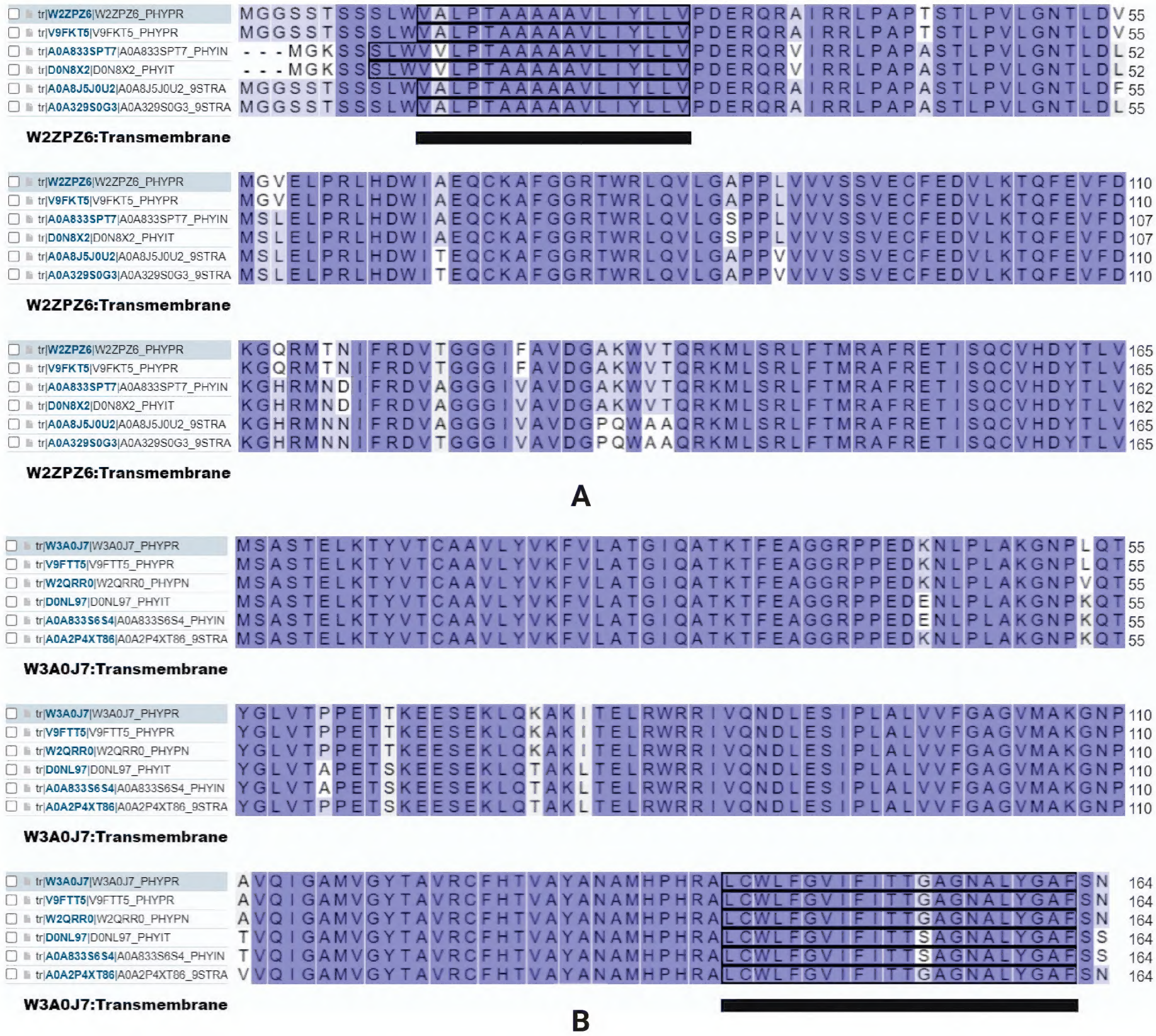


Figure 4. Example of multiple alignments of CYP450 and GST of Phytophthora. Fragments from 1 to 165 amino acid residues of six different CYP450 (**A**) and sequences of six different GSTs (**B**) are shown. Amino acid residues are labeled in fasta format. Transmembrane regions are circled in black.

Table 2. Binding energy values of intermolecular interaction between ligands (fungicide) and receptors (enzyme) during complex formation.

Receptor, ID UniProtKB	Conformation rank	Minimum binding energy (kcal/mol)	Conformation rank	Minimum binding energy (kcal/mol)
	Fluopicolide		Propamocarb	
Cytochrome P450 ID: A0A833SPT7	1	-9.53	1	-6.73
	2	-9.13	2	-6.10
	3	-9.13	3	-6.05
	4	-8.74	4	-5.79
	5	-8.65	5	-5.66
			6	-5.26
Glutathione S transferase ID: D0NL97	1	-7.87	1	-5.96
	2	-7.65	2	-5.26
	3	-7.43	3	-5.06
	4	-6.87		
	5	-6.70	4	-4.82
	6	-6.70		

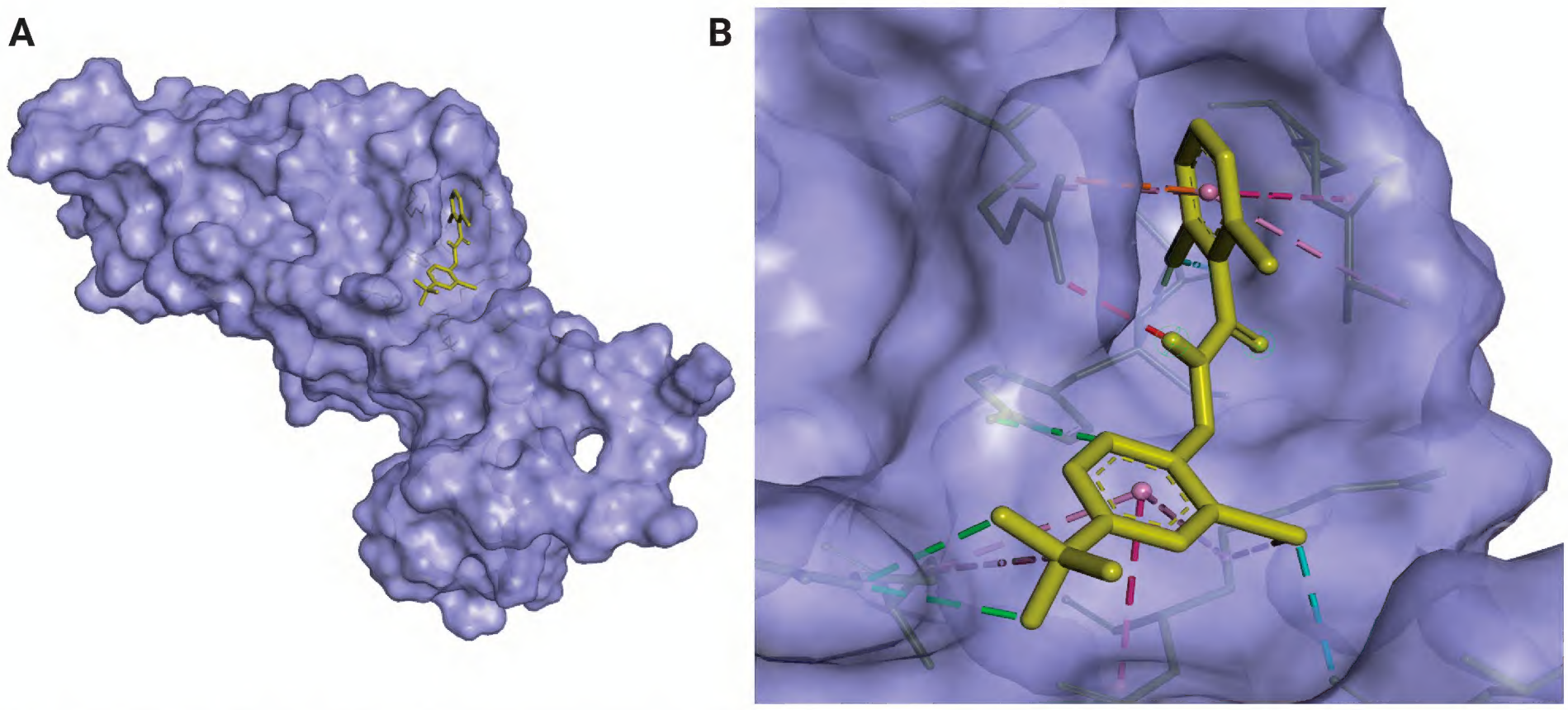


Figure 5. Example of a modeled ligand-receptor complex formed between GST and fluopicolide **A** general view of the complex **B** focus on the ligand. GST is depicted as a structure with a single molecular surface in purple; fluopicolide is depicted as a rod-like model in yellow.

number of conformations (6 each) was obtained for CYP450-propamocarb and GST-fluopicolide complexes, the minimum (4) for GST-propamocarb complexes.

Quantitative assessment of the free energy of binding of protein-ligand complexes is of great importance in determining the biological activity of the ligand (Baskin et al. 2009). Thus, the lowest minimum binding energy (-9.53 kcal/mol) is possessed by the CYP450-fluopicolide complex, the highest energy – by the GST-propamocarb complex (-4.82 kcal/mol). The difference between the minimum binding energies of propamocarb and fluopicolide complexes is 29.4% for CYP450, and 24.3% for GST. The difference between the maximum binding energies of the fungicide complexes is 39.2% for CYP450, and 28.1% for GST. The maximum difference in binding energies between the conformation ranks of the complexes of fluopicolide and propamocarb were 9.2% and 21.8% for CYP450, and 14.9% and 19.1% for GST, respectively.

In general, the modeling showed that the value of the minimum binding energy is lower for each complex of the target protein with fluopicolide (-9.53 to -6.7) than with propamocarb (-6.73 to -4.82). In addition, the difference in minimum binding energies between the conformation ranks of the complexes is markedly lower for fluopicolide compared to propamocarb complexes. This demonstrates a higher probability of interaction and formation of a stable complex between the targets and the fungicide fluopicolide than between the target and propamocarb.

At the same time, the obtained values of the minimum binding energy indicate high stability of all modeled herbicide-enzyme complexes. This is also indirectly evidenced by the number of potential positions (no more than 5, 6 for each complex), which means that there is a high probability of a closer interaction between the ligand and the given protein site.

In addition to high formation potential, the modeled complexes had potential high stability due to the formation of various bonds between ligands and polypeptide chains of proteins: hydrogen bonds, hydrophobic bonds, alkyl bonds, van der Waals forces, and so on (Fig. 6). The formation of 3 to 8 different types

of bonds was observed in different complexes. Modeling showed that from 8 to 17 amino acid residues of different complexes were bound to ligands during the formation of the complexes. For the CYP450-fluopicolide complex, these are alanine, arginine, histidine, methionine, leucine, asparagine, valine, serine, cysteine, tryptophan, and proline. For the CYP450-propamocarb complex, it is histidine, asparagine, valine, serine, cysteine, tryptophan, isoleucine, and phenylalanine. For the GST-fluopicolide complex, these are alanine, arginine, tyrosine, histidine, methionine, and leucine. For the GST-propamocarb complex it is alanine, arginine, tyrosine, methionine and leucine. For all complexes, a

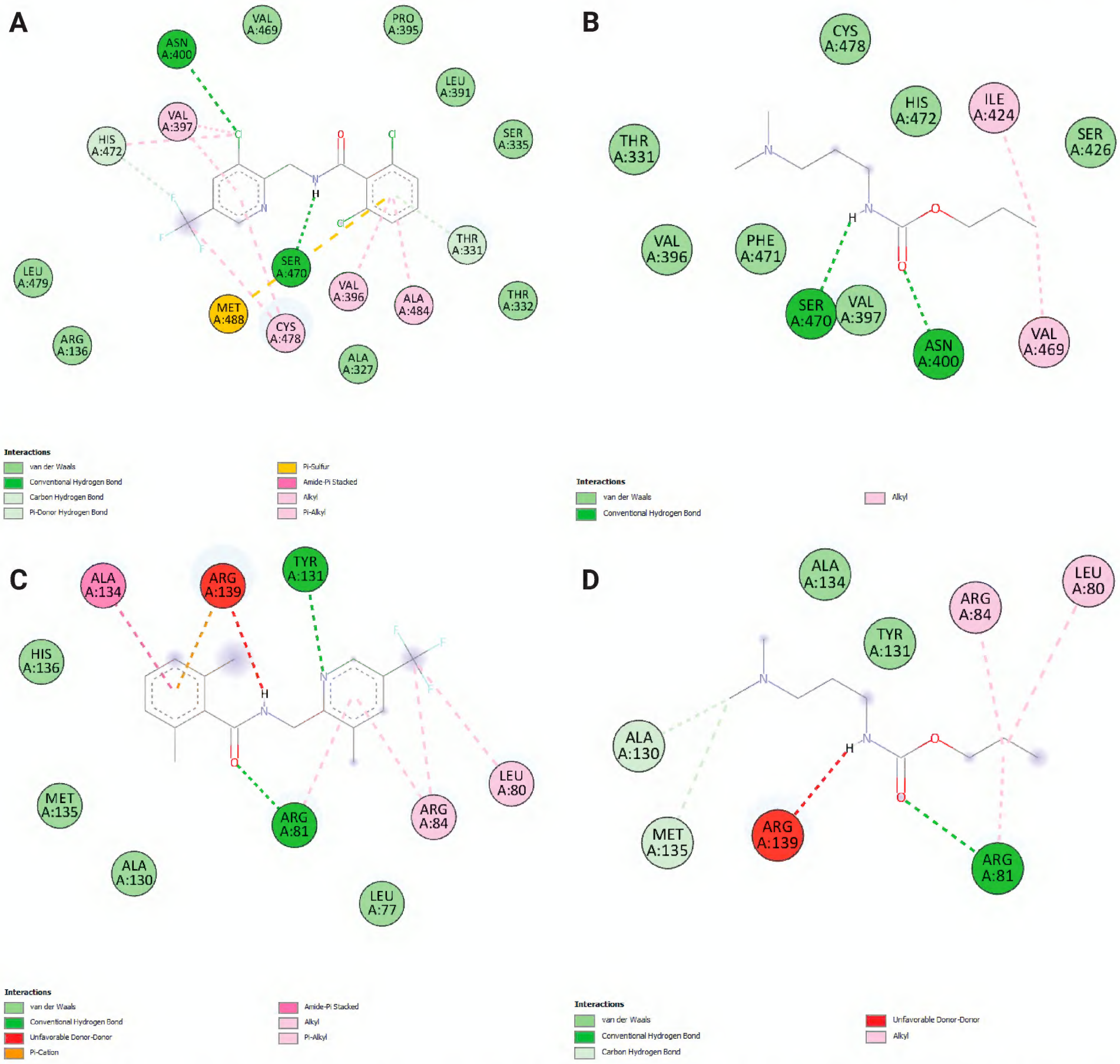


Figure 6. 2D interaction of pesticides and proteins with bond involved in the formation of the complex. Fluopicolide with cytochrome P450 (**A**), propamocarb with cytochrome P450 (**B**), fluopicolide with glutathione S transferase (**C**), propamocarb with glutathione S transferase (**D**). Colored circles indicate amino acid residues of polypeptide chains involved in intermolecular interaction. The name of amino acid residues is indicated by common abbreviations: alanine (ALA), arginine (ARG), tyrosine (TYR), histidine (HIS), methionine (MET), leucine (LEI), asparagine (ASP), valine (VAL), serine (SER), cysteine (CYS), tryptophan (THR), isoleucine (ILE), proline (PRO), and phenylalanine (PHE). The sequence number of the amino acid in the protein chain is labeled A:469.

quantitative predominance of aliphatic amino acids involved in the binding of fungicide molecules is shown.

The CYP450-fluopicolide complex shows the greatest diversity of bonding types with the predominance of electrostatic interaction of molecular shells, while the CYP450-propamocarb complex shows the least diversity.

For fluopicolide and propamocarb, an increase in the minimum binding energy values was observed with an increase in the number of amino acid residues involved in the formation of pesticide-protein complexes.

CYP450 of *P. infestans* is a membrane protein consisting of 532 Am. However, only a minor portion of it (6–25 Am) is immersed in the membrane, and docking with the ligand was shown on the C-terminal side. The site (478 Am) with which the ligand interacted is responsible for heme binding (cofactor). GST of *P. infestans* belongs to membrane enzymes consisting of 532 Am. Unlike CYP450, GST has a transmembrane site (141–162 Am) located at the C-terminal end of the polypeptide chain. Docking with fungicides is shown on the opposite side of the enzyme in the N-terminal domain at the site of the G-site (glutathione binding site). Thus, blocking the operation of these sites of the enzymes under study is likely to result in impaired function of these proteins.

No previous studies have been conducted using molecular docking to analyze the molecular interactions of fluopicolide and propamocarb with GST, cytochrome P450, and glutathione S transferase. However, molecular docking methods have been used to search for hypothetical targets for these fungicides (Thomas et al. 2018; Dai et al. 2024).

Conclusions

The data acquired in this study strongly point towards a greater propensity for forming stable ligand-receptor complexes with fluopicolide in comparison to propamocarb when considering all the presented target proteins. This compelling finding suggests that fluopicolide fungicide could be a more advantageous option for effectively controlling the phytopathogen *P. infestans*.

It is noteworthy that the results obtained from our research and the algorithm we have developed are characterized by a high degree of impartiality. This inherent objectivity renders them readily applicable for adoption by fellow researchers in the field of bioinformatics for their own experiments and investigations.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statement

No ethical statement was reported.

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Author contributions

Pavel Timkin and Igor Pamirsky made crucial contributions to the computations and writing of the paper. Yusufjon Gafforov, Mengcen Wang, Kun Qiao and Alisher Ajiev were engaged in methodological support of the paper. Kirill Golokhvast supervised the implementation of the pro-ject.

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Data availability

All of the data that support the findings of this study are available in the main text.

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